# Reply to Agger and Kowalski

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DOI: https://doi.org/10.1086/651691

# Correspondence

## Chronic Granulomatous Disease, Catalase, and *Actinomyces*

To the Editor—We read with interest the article "*Actinomyces* in Chronic Granulomatous Disease: An Emerging and Unanticipated Pathogen" by Reichenbach et al [1]. However, we do not believe this series of patients with chronic granulomatous disease (CGD) and *Actinomyces* infection demonstrates compelling evidence to dismiss the traditionally recognized risk factor of microbial catalase as the most important virulence factor in patients with CGD unless phenotypic-negative catalase results from the species isolated in this series are made available.

*Actinomyces* infection in patients with CGD should not necessarily be considered as supporting evidence for a different mechanism of virulence, because *Actinomyces* species are not universally catalase negative, as was suggested in the article [1]. It is notable that, of the 8 *Actinomyces* isolates identified to the species level, 7 were identified as *Actinomyces naeslundii* (6 specimens had positive culture results, and 1 specimen had positive serological test results). The genospecies type 2 of *A. naeslundii* is catalase-positive in ~55% of isolates, and 30% of all genospecies isolates of *A. naeslundii* were catalase positive in one dental study [2]. Occasionally, other *Actinomyces* species can be catalase positive, as well [3]. In a recent review of 92 clinically significant strains of *Actinomyces* species identified by 16S ribosomal DNA analysis, no isolates were identified as *A. naeslundii*, which highlighted the infrequency of this organism as a cause of clinically significant disease in patients without CGD [4].

Without this essential biochemical data, the conclusion that the "susceptibility of patients with CGD to infection with catalase-negative *Actinomyces* species confirms that catalase production is neither necessary nor sufficient for microbial virulence in CGD" is not supported by this article [1, pp 1708–1709]. Rather, catalase positivity, which is frequently found in *A. naeslundii,* may still explain most of these infections. In conclusion, this series may not significantly depart from the traditional association of catalase-positive microbial infections and CGD. Although catalase-negative infections in patients with CGD have been described, the frequency of such infections, compared with those due to catalase-producing organisms, and the importance of alternative mechanisms require further investigation.

### Acknowledgments

***Potential conflicts of interest.*** W.A.A. and T.J.K.: no conflicts.

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**Clinical Infectious Diseases 2010; 50(9):1325**

1058-4838/2010/5009-0020$15.00
DOI: 10.1086/651690

## Reply to Agger and Kowalski

To the Editor—We appreciate the comments of Drs Agger and Kowalski, which echo the traditional assumption that microbial catalase production is the "most important virulence factor in patients with chronic granulomatous disease [CGD]" [1, p. 1325]. They rightly point out that *Actinomyces* can be variable in terms of catalase production, and although the majority of strains are catalase negative, a significant number may be catalase intermediate or even catalase positive. However, because *Actinomyces* are generally considered to be catalase negative, and because most are, we thought it important to point out that they do, in fact, cause significant morbidity in CGD. Although it is true that most pathogens associated with CGD are catalase positive, that is a general truism applicable to all pathogens that affect humans: most pathogens are catalase producing, with the broad exception of the streptococci. We cited several strong lines of clinical and basic evidence that support our assertion that catalase is not per se a necessary virulence factor in CGD infections. First, deletion of catalase from *Staphylococcus aureus* did not change its virulence in a mouse model of CGD [2]. Second, deletion of catalase from *Aspergillus nidulans* did not change its virulence in a mouse model of CGD [3]. Third, numerous case reports and cases from our current series are clearly caused by catalase negative organisms, negating catalase as a necessary virulence factor in CGD [4]. Drs Agger and Kowalski are correct that we did not study every strain of *Actinomyces* for catalase production, and there are indeed catalase-positive strains of *Actinomyces naeslundii.* We did study the National Institutes of Health–isolated strains for catalase production with use of standard techniques and found them (from patients 3, 4, 5, and

8 [5]) to be catalase negative. Therefore—although the allure of the catalase hypothesis is strong, its directness of explanation is soothing, and it has long-standing prominence in the field—the clinical and laboratory evidence overwhelmingly indicates that catalase is neither necessary nor sufficient for virulence in CGD.


## Acknowledgments

***Potential conflicts of interest.*** S.M.H. and J.R.: no conflicts.



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**Clinical Infectious Diseases 2010; 50(9):1325–1326**



DOI: 10.1086/651691


## Staphylococcal Toxic Shock Syndrome, Superantigenicity, and Hypersensitivity

To the Editor—With great interest, we read the article by Chandy et al [1] concerning staphylococcal toxic shock syndrome (TSS) and its association with superantigenicity and hypersensitivity. The authors describe a 16-year-old girl who presented with severely acidotic hyperglycemia and concomitant *Staphylococcus* bacteremia, with accompanying TSS without rash or desquamation. Blood and urine cultures revealed methicillin-susceptible *Staphylococcus aureus.* The patient was treated with clindamycin for 5 days, cefazolin for 14 days, and immunoglobulin (1 mg/kg).

The authors state that 10% of *S. aureus* strains produce enterotoxin, but the prevalence of TSS is much lower than 10%. Another explanation for this clinical picture is septic shock associated with community-acquired *S. aureus* bloodstream infection. Furthermore, the enterotoxin production could be an innocent bystander. Also, the patient did not meet the criteria for TSS because there was no rash or desquamation, but she did meet the criteria for community-acquired *S. aureus* bloodstream infection [2]. Given the limited clinical evidence for efficacy of immunoglobulin and clindamycin for the treatment of staphylococcal TSS, it seems unlikely that there was a causal relationship between the administration of clindamycin and immunoglobulin and the hemodynamic improvement after administration.

Therefore, we concluded that this patient had a complicated *S. aureus* bloodstream infection that was acquired in the community [2, 3]. This infection has a high risk of hematogenous complications, and although there was no accompanying endocarditis, a recent review in this journal recommended at least 4 weeks of high-dose anti-staphylococcal penicillin for community-acquired *S. aureus* bloodstream infection [2, 3]. The associated urine culture also grew *S. aureus,* and the patient had type 1 diabetes. Both factors are also associated with hematogenous complications and, possibly, provide an extra argument in favor of at least 4 weeks of high-dose therapy [4, 5].


## Acknowledgments

***Potential conflicts of interest.*** G.W.D.L. amd P.H.G.: no conflicts.



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**Clinical Infectious Diseases 2010; 50(9):1326**



DOI: 10.1086/651692


## Reply to Landman and Groeneveld

To the Editors—We appreciate the interest of Landman and Groeneveld [1] in our study. They note that the child described in our article may have had septic shock due to community-associated *Staphylococcus aureus* infection rather than staphylococcal toxic shock syndrome (TSS). We cannot state definitively that the child had staphylococcal TSS, because all of the diagnostic criteria for staphylococcal TSS other than erythroderma and desquamation—the 2 criteria that the patient lacked—are common to both TSS and septic shock. It is also noteworthy that the presence of septic shock does not preclude the patient from having TSS. Although the majority of patients with staphylococcal TSS do not have blood cultures positive for *S. aureus,* a significant